EXHIBIT 2

UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF TEXAS
MARSHALL DIVISION

ERFINDERGEMEINSCHAFT UROPEP GbR, **Plaintiff,** **vs.** **ELI LILLY AND COMPANY, and BROOKSHIRE BROTHERS, INC.,** **Defendants.**	**Case No. 2:15-cv-01202-JRG-RSP**

DEFENDANTS' INVALIDITY CONTENTIONS

Pursuant to Local Patent Rule ("P.R.") 3-3 and 3-4 and this Court's Order (Dkt. 65), as amended (Dkt. 71), Defendants Eli Lilly and Company and Brookshire Brothers, Inc. ("Defendants") hereby serve their Invalidity Contentions on Plaintiff Erfindergemeinschaft UroPep GbR ("Plaintiff"). These Invalidity Contentions address only the claims of U.S. Patent 8,791,124 (the '124 Patent) that were asserted in Plaintiff's Local Rule 3-1 and 3-2 Disclosures ("Plaintiff's Infringement Contentions") served on November 24, 2015, *viz.* Claims 1 and 3 of the '124 Patent (the "Asserted Claims").

I. INTRODUCTION AND RESERVATION OF RIGHTS

These Invalidity Contentions are based on information reasonably known and available to Defendants at this time and are subject to revision as discovery proceeds. Moreover, these Invalidity Contentions are based on the limited information provided by Plaintiff in its Infringement Contentions. Despite obligations under the Local Rules and the Court's Scheduling Order, Plaintiff's Infringement Contentions fail to provide sufficient detail concerning the

meaning and scope of the Asserted Claims and how the claim language in fact applies to the activities of the Defendants. Plaintiff's Infringement Contentions also fail to show how each individual Defendant can be liable for inducement of infringement of the claimed method of treatment in the '124 Patent or direct infringement of the identified claims. Defendants accordingly reserve the right to amend and/or supplement these Invalidity Contentions, including the right to identify additional information concerning the prior art identified herein as well as additional prior art after entry of this Court's claim construction of the Asserted Claims.

Furthermore, Defendants have not yet received all relevant discovery, including documents, from Plaintiff or the named inventors of the '124 patent (each of whom are "partners" of Plaintiff), relating to the claims or defenses in this action. For example, Plaintiff has not produced all documents evidencing the conception or reduction to practice of any purported invention claimed in the '124 Patent. Defendants have also not had the opportunity to take any deposition in this action, including the depositions of the named inventors and partner/owners of Plaintiff. To the extent that Defendants obtain additional information through discovery of Plaintiff or of third parties which may impact the scope and meaning of the claims, Defendants reserve the right to supplement or amend these Invalidity Contentions. Defendants further reserve the right to introduce and use such supplemented materials at trial.

As noted above, the Asserted Claims have not been construed. These Invalidity Contentions cannot reasonably seek to predict Plaintiff's proposed claim constructions or the Court's ruling on claim construction, and, therefore, are not and should not in any way be seen as admissions or adoptions of any particular claim scope or construction, or an admission that any particular limitation is met in any particular way by the conduct Plaintiff contends infringes the Asserted Claims. Nothing herein should be construed as an admission that Defendants agree with

Plaintiff's reading of the Asserted Claims on any conduct of either Defendant described in the Infringement Contentions, or any implied construction of the Asserted Claims by Plaintiff in Plaintiff's Infringement Contentions.

However, Defendants' Invalidity Contentions seek to provide as complete a disclosure as possible in advance of the claim construction process where the parties will confer regarding the proper constructions of the terms. Given that the Court has not yet made any claim construction ruling in this action, and the parties have not yet specifically identified terms for construction or exchanged proposed constructions under the applicable rules, Defendants' Invalidity Contentions are based in whole or in part on their present understanding of Plaintiff's contentions concerning the scope and construction of the Asserted Claims. Defendants reserve the right to interpret the Asserted Claims differently over the course of the litigation, and do not adopt any interpretations impliedly or expressly put forth in these contentions. Accordingly, Defendant's Invalidity Contentions, including the invalidity claim charts, may reflect alternative positions as to claim construction and scope.

Plaintiff has also failed to present any contentions for infringement under the doctrine of equivalents, stating only "To the extent any element or limitation of any Asserted Claim is not found to have literal correspondence with the Accused Instrumentality, [Plaintiff] alleges that any such elements or limitations are equivalently present with respect to the Accused Instrumentality." *See* Plaintiff's Infringement Contentions at 3. Plaintiff's failure to provide detailed infringement contentions that identify each specific claim limitation allegedly infringed under the doctrine of equivalents and its alleged equivalent element in the Accused Instrumentalities, or any bases for purported insubstantial differences between each such limitation and its alleged equivalent. Plaintiff should be foreclosed from amending Plaintiff's

Infringement Contentions to make any such equivalence arguments because permitting such amendments would cause undue prejudice to Defendants.

Based on the information available at this time, and the literal scope of the Asserted Claims read in view of the intrinsic evidentiary record, Defendants contend that the Asserted Claims are invalid under 35 U.S.C. § 102 and/or § 103 as being anticipated by or rendered obvious by prior art disclosed herein. Prior art not included in this disclosure, whether or not now known to Defendants, may become relevant depending on the claim constructions ultimately adopted by the Court. Defendants' ongoing investigation may also uncover additional prior art references or activities. Any obviousness combinations of references provided herein pursuant to 35 U.S.C. § 103 are not intended to be exhaustive. Additional obviousness combinations of the references identified below are possible, and Defendants reserve the right to use any such combinations in this litigation.

In addition, or in the alternative, Defendants contend that the Asserted Claims do not satisfy one or more requirements of 35 U.S.C. § 112. Nevertheless, in the invalidity claim charts, Defendants have endeavored to apply the claim scope apparently attributed by Plaintiffs in their Infringement Contentions for terms Defendants contend are indefinite and/or otherwise fail to meet the requirements of 35 U.S.C. § 112. The application of prior art in these Invalidity Contentions should not be construed as an admission that Defendants agree that any of the Asserted Claims satisfies the requirements of 35 U.S.C. § 112.

Finally, Defendants contend that the Asserted Claims are directed to laws of nature that are not eligible for patenting. The Asserted Claims are, therefore, invalid under 35 U.S.C. § 101.In the invalidity claim charts, Defendants have endeavored to apply the claim scope apparently attributed by Plaintiffs in their Infringement Contentions to the claims at issue. The

application of prior art in these Invalidity Contentions should not be construed as an admission that Defendants agree that any of the Asserted Claims satisfies the requirements of 35 U.S.C. § 101.

The foregoing statements and reservations of rights are hereby expressly incorporated by reference in their entirety into each of the disclosures below, into the invalidity charts served herewith as Exhibits, and into each disclosure corresponding to each element of every claim whether contained herein or within any exhibit.

II. STATEMENT AS TO ALLEGED PRIORITY DATE OF THE '124 PATENT

Plaintiff contends that all of the Asserted Claims are entitled to "a priority at least as early as July 19, 1997" (*see* Plaintiff's Infringement Contentions at 4), which is the filing date of application No. PCT/EP97/03617, to which the '124 Patent claims priority. For purposes of these Invalidity Contentions, Defendants rely on various documents and references as prior art based upon Plaintiff's alleged priority date of July 19, 1997. However, these Invalidity Contentions should not be taken as an admission that Plaintiff's alleged priority date is correct or admitted as such by Defendants either expressly, or on an implied basis. Defendants specifically reserve the right to challenge any asserted priority date.

The '124 Patent issued from application No. 13/339,561 filed on December 29, 2011, which is a continuation of application No. 10,443,870 filed on May 23, 2003, now U.S. Patent No. 8,106,061, which is a continuation of application No. 09,462,090 filed as application No. PCT/EP97/03617 on July 19, 1997, now abandoned. Defendants contend that the Asserted Claims are not entitled to the benefit of the filing date of the '124 Patent (or the priority date of the '090 application or any other application noted in the priority claim) because the subject matter of the Asserted Claims is not disclosed in the manner required by 35 U.S.C. § 112, first

paragraph, in the earlier filed related patents or applications. *See, e.g., In re NTP, Inc.*, 654 F.3d 1268, 1277 (Fed. Cir. 2011).

> Nothing in 35 U.S.C. §§ 301 *et seq.* entitles a patentee to a claim of right to its earliest priority date. Under § 120, a patent is entitled to the priority date of an earlier filed application if (1) the written description of the earlier filed application discloses the invention claimed in the later filed application sufficient to satisfy the requirements of § 112; (2) the applications have at least one common inventor; (3) the later application is filed before the issuance or abandonment of the earlier filed application; and (4) the later application contains a reference to the earlier filed application. In addition, if the later filed application claims priority through the heredity of a chain of applications, each application in the chain must satisfy § 112. *Lockwood v. Am. Airlines*, 107 F.3d 1565, 1571 (Fed. Cir. 1997).

In re NTP, 654 F.3d at 1277. Defendants contend that Plaintiff cannot claim priority to the PCT application filed July 9, 1997 (or any other application in the chain), but instead is restricted to the priority date of December 29, 2011, which is the the filing date of application No. 13/339,561 that eventually issued as the '124 Patent.

To the extent that the '124 Patent is not afforded the claimed priority date of July 9, 1997, Defendants reserve the right to amend these Invalidity Contentions and to rely on the parent or related patents and applications of the '124 Patent as well as the Accused Instrumentality and/or Defendants' previously existing patents and patent applications as prior art. By way of example, however, the Asserted Claims of the '124 Patent would be anticipated by numerous references[1] and publications and studies relating to Lilly's own accused product, Cialis® (tadalafil).[2]

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[1] *E.g.*, Canadian Patent Application, CA 2287122, to Michale Grant Wylliee, filed October 19, 1999, published April 21, 2000, titled "Treatment of BPH with cGMP elevators"; S.A. Kaplan and R.R. Gonzalez, "Phosphodiesterase Type 5 Inhibitors for the Treatment of Male Lower Urinary Tract Symptoms" Rev Urol. 2007 Spring; 9(2): 73-77.

[2] On December 3, 2010, Lilly filed a supplemental NDA application with the FDA proposing new indications for Cialis®, including the treatment of the signs and symptoms of BPH, as well as the signs and symptoms of BPH when occurring with the signs and symptoms of ED. On October 6, 2011, the FDA approved Cialis® to treat the signs and symptoms of BPH, as well as the signs and symptoms of BPH when occurring with ED.

III. IDENTIFICATION OF PRIOR ART

In addition to the references cited on the face of the '124 Patent and any patents or applications that claim priority to, priority from, or are the basis for a claim of priority in the '124 Patent (collectively, the "Related Patents"), the admitted prior art in the specification of the '124 Patent and Related Patents and the prosecution histories of the '124 Patent and Related Patents, Defendants hereby identify prior art references in Exhibits A-1 through A-57 (hereinafter referred to as "Exhibit A") the relevance of which is described in greater detail herein and within the exhibits themselves.

The '124 Patent is governed by the pre-AIA statutory sections of 35 U.S.C. §§ 102, 103 and 112.

Certain prior art references disclose all of the elements of the Asserted Claims either explicitly or inherently and, therefore, anticipate the Asserted Claims under 35 U.S.C. 102, or render the Asserted Claims obvious under 35 U.S.C. 103, including obviousness stemming from a single prior art reference and the teachings conveyed by that reference in view of the skill of those of ordinary skill in the art, or via a combination of prior art references in view of the skill of those of ordinary skill in the art. Defendants further note that each and every prior art reference may also be relied upon to show the state of the art in the relevant time frames.

Defendants hereby reserve the right to make additional disclosures, including raising additional anticipation arguments based on information learned in discovery. Discovery may reveal information that affects the disclosures and contentions herein, and upon that discovery, Defendants reserve the right to update these disclosures and contentions, as appropriate. Moreover, the obviousness combinations of references provided below under 35 U.S.C. § 103 are merely exemplary and are not intended to be exhaustive. Additional obviousness

combinations of the references identified below are possible, and Defendant reserves the right to use any such combination(s) in this litigation.

IV. INVALIDITY CONTENTIONS PURSUANT TO P.R.3-3

A. Contentions under P.R. 3-3(a)-(c)

1. Introduction

Plaintiff has served each Defendant with Infringement Contentions alleging infringement of the'124 Patent. Specifically, Plaintiff has alleged that each Defendant infringes claims 1 and 3 of the '124 Patent. Because the Patent Rules require that a defendant accused of infringement set forth invalidity contentions with regard to the claims asserted against it, *see* P.R. 3-3(a), each Defendant joins in these contentions for each Asserted Claim. Pursuant to the Patent Rules, Defendants do not provide any contentions regarding any claims not asserted against at least one Defendant. To the extent the Patent Rules and/or the Court permit Plaintiff to assert additional claims against Defendants in the future, each Defendant reserves all rights to join in the Invalidity Contentions regarding such claims, or to disclose new or supplemental Invalidity Contentions regarding such claims.

Defendants contend that the Asserted Claims are invalid as anticipated by the prior art under 35 U.S.C 102 and/or as obvious in view of the prior art, the knowledge of a person having ordinary skill in the art, and/or secondary factors of obviousness under 35 U.S.C. 103. Defendants organize the prior art by primary reference, including admitted prior art, and reserve the right to rely on any identified piece of prior art individually to anticipate each of the Asserted Claims and/or to render obvious each of the Asserted Claims in view of the knowledge of one having ordinary skill in the art or in combination with other references identified herein. The analysis reflected in these contentions reflects Defendants' understanding of the proper claim

construction. To the extent claim construction is different than understood, many of the 103 prior art references could be anticipatory references and vice versa.

The charts attached as Exhibits A-1 through A-57 to these Invalidity Contentions specifically point out, as non-limiting examples, where the prior art identified by Defendants discloses, either expressly or inherently, and/or renders obvious each element of the Asserted Claims. Defendants have endeavored to cite to the most relevant portions of the identified prior art. However, other portions of the identified prior art may additionally disclose, either expressly or inherently, and/or render obvious one or more elements of the Asserted Claims. Although Defendants have not cited to those other portions to avoid excessive, cumulative citations, Defendants reserve the right to rely on those uncited portions of the identified prior art as further evidence for the invalidity of the Asserted Claims. Moreover, Defendants reserve the right to rely on any evidence, including expert testimony, to provide context to or aid in understanding the cited portions of the identified prior art. Where Defendants cite to a particular drawing or figure, the citation encompasses the description of the drawing or figure, as well as any text associated with the drawing or figure. Similarly, where Defendants cite to particular description of or text associated with a drawing or figure, the citation encompasses the associated drawing or figure as well.

Certain pieces of identified prior art inherently disclose features of the Asserted Claims. Defendants reserve the right to rely on inherency to demonstrate the invalidity of the Asserted Claims. Defendants may rely on any evidence, including expert testimony, to establish the inherency of certain features of the prior art to invalidate the Asserted Claims. Defendants also reserve the right to rely on any evidence, including expert testimony, to prove that the solutions

or prior art cited herein are enabled or to explain the meaning of a term used in the solutions or any prior art cited herein.

The Asserted Claims are also obvious because they merely use known scientific and natural principles and apply that knowledge for treatment of a symptom or disorder, the result of which would be known to a person of ordinary skill in the art based on the knowledge of the tissue composition of the urogenital system as well as the role of PDEs and the impact of PDE inhibitors on smooth muscle tissue. The claimed method in the Accused Claims performs the same function that had been known, to perform and yield no more than what one having ordinary skill in the art would expect from an organ system containing smooth muscle tissue. At the time of the purported invention, there were a finite number of phosphodiesterases.

Short name	*PDE isoenzyme gene family*	*Alternative names*
PDE1	Calmodulin-dependent PDEs	CaM-PDE, PDE I
PDE2	Cyclic GMP-stimulated PDEs	cGS-PDE, PDE II
PDE3	Cyclic GMP-inhibited PDEs	cGI-PDE, PDE III
PDE4	Cyclic AMP-specific PDEs	RD, DPD, PDE IV
PDE5	Cyclic GMP-specific PDEs	cGB-PDE, PDE V
PDE6	Photoreceptor PDEs	ROS/COS-PDE, PDE VI
PDE7	High affinity, cyclic AMP-specific PDE	HCP1, PDE VII

Reference

Beavo, J.A., Conti, M. and Heaslip, R.J. (1994). ASPET meeting report: multiple cyclic nucleotide phosphodiesterases. Mol. Pharmacol. 46, 399–405.

In addition, it was known at the time of the purported invention that PDE V existed in various smooth muscle and a functional outcome associated with the inhibition of PDE V had been demonstrated, including relaxation of smooth muscle. It also was well known to treat symptoms associated with BPH by relaxation of the smooth muscle of the prostate through medical treatments. Accordingly, it would have been obvious to a person of ordinary skill in the art to pursue the known therapeutic target for treating BPH by relaxing prostatic smooth muscle by using a PDE V inhibitor.

Further, a person skilled in the art would have been familiar with all of the claim elements that the patentee used to distinguish the prior art during prosecution. The identified prior art references merely use those familiar elements for their primary or well-known purposes and in a manner well within the ordinary level of skill in the art. Accordingly, common sense and the knowledge of one having ordinary skill in the art, as evidenced by the prior art, render the Asserted Claims invalid.

With regard to the prior art that Defendants identify as rendering the Asserted Claims obvious, the reasons or motivation to combine the prior art include the fact that all of the prior art is in the field of the treatment and prevention of diseases and disorders involving smooth muscle tissue, including art that shows the ability of a drug to induce smooth muscle relaxation in various organs of the urogenital system, including the prostate, as a way to relieve BPH symptoms, the role of PDEs in the function of the smooth muscle tissue and the use of specific PDEs to impact that role and effect smooth muscle function, and the knowledge of the identity of specific PDE inhibitors which would achieve the desired effect of relaxing smooth muscle and/or treating symptoms of BPH. In seeking a potential method of treatment, or prevention, of a urogenital disorder involving symptoms associated with BPH, one of ordinary skill in the art tasked with seeking a method of treatment or prevention would be motivated to investigate the various existing PDE inhibitors as well as patents, and other publications identified herein to address the particular needs. The combinations and modifications of the prior art to invalidate the Asserted Claims would have arisen from ordinary experimentation, ordinary skill, or common sense and/or would have been obvious to try or otherwise predictable in the field of treatment of urogenital disorders such as BPH. A person having ordinary skill in the art would have been motivated to combine the prior art based on the nature of the problem to be solved, the teachings

of the prior art, and the knowledge of persons having ordinary skill in the art. Moreover, other market forces (such as the desire to obtain medical, non-invasive, and less expensive treatments for treating a large portion of the male population) would have prompted one of skill in the art to seek known medical treatments for a similar therapeutic target and apply that to reach the purported invention. Additionally, some pieces of prior art refer to or discuss other pieces of prior art, illustrating the close relationships among the prior art. To the extent that any piece of prior art refers to or discusses another piece of prior art, either expressly or inherently, it would have been obvious to combine those prior art references for at least that reason.

Although certain pieces of prior art are listed as evidence for particular prior art solutions, certain of those pieces of prior art, as well as other literature, publication, and knowledge of persons of skill in the art, describe, relate to, and are evidence of other prior art solutions that render the Asserted Claims invalid. Defendants reserve the right to rely on any identified piece of prior art as evidence supporting any of those other prior art solutions.

To the extent that Plaintiff argues that a piece of prior art does not disclose an element or challenges a combination of prior art identified by Defendants, Defendants reserve the right to supplement these Invalidity Contentions to address that argument or challenge. Defendants may rely on any combination of the prior art disclosed in these Invalidity Contentions, including the charts attached hereto as Exhibits A-1 through A-57, the knowledge of those skilled in the art, and/or other prior art to show that it would have been obvious to include the allegedly missing element or to further buttress the motivation to combine the prior art. Defendants' ability to supplement or amend these Invalidity Contentions may depend on when Defendants receive any rebuttal from Plaintiff.

2. Admissions in the Specification or Prosecution History of the '124 Patent

In addition to the prior art identified below and the accompanying invalidity claim charts, Defendants also plan to rely on the "Background of the Invention" and other relevant portions of the '124 Patent, the prosecution history of the '124 Patent (including the cited references) and the prosecution histories of related patents, and fact and expert testimony about the prior art, to prove that the Asserted Claims are anticipated and/or rendered obvious under 35 U.S.C. §§ 102 and 103.

The specification of the '124 Patent makes clear that the claims are directed to a mechanism of action that occurs naturally within the human body, "namely the affection of a key enzyme within the smooth muscle cells of the prostate gland, phosphodiesterase." '124 Patent, Col. 1:34-35. According to the '124 Patent:

> The physiological transmission of information for the relaxation of smooth muscle cell is effected by messengers of the blood (hormones) or the nerves (neurotransmitters). These messengers and neurotransmitters cause an increase in the levels of the cyclic nucleotides "cyclic adenosine monophosphate" (cAMP) and "cyclic guanosine monophosphate" (cGMP) in the smooth muscle cell, resulting in relaxation. cAMP and cGMP themselves are hydrolyzed by phosphodiesterase's (PDEs). Inhibitors of PDEs in turn reduce the digestion of cAMP and cGMP, resulting in the increase of these molecules within the cell and thus in a relaxation of the smooth muscle cell.

Id. at Col. 1:36-47. It is further acknowledged in the '124 Patent that the foregoing mechanism of action is well known. *Id.* at Col. 1:47-51. The specification of the '124 Patent claims that it has been found that three specific PDE isoenzymes—PDE I, PDE IV and PDE V—"are of particular importance in human prostatic muscles." *Id.* at Col. 2:6-8; *see also* Col. 2:8-11 ("After performing Q-sepharose chromatography, there has been found a typical pattern of the human prostatic tissue showing the presence of the PDE isoforms I, IV and V (below)." Independent Claim 1 purports to claim merely "an inhibitor of phosphodiesterase (PDE) V" for the

"prophylaxis or treatment of benign prostatic hypertrophy." As admitted in the specification, PDE V is a known enzyme which plays a key role in the hydrolysis of cGMP in smooth muscle tissue. It is also known that inhibition of the activity of PDE V may result in an increase in cGMP and the subsequent relaxation of the smooth muscle tissue. In addition, the relaxation of smooth muscle in the prostate and other organs of the urogenital system was known to treat symptoms of BPH; drugs (such as alpha blockers) had been used for years to achieve this therapeutic target. In addition, natural products (such as plant extracts, herbal medicines, and foodstuffs) had been consumed for centuries for BPH and related urogenital disorders and symptoms. As it was known to persons of ordinary skill in the art to use PDE inhibitors, and specifically PDE V, to relax smooth muscle tissue to treat and prevent symptoms associated with the urogenital system, such as BPH, the admitted prior art anticipates or renders obvious that which is claimed in Claims 1 and 3, either alone or in combination with the exemplary prior art references cited above.

The motivation to combine such art may be found at least in (a) the art itself (e.g., discussing the use of phosphodiesterase V inhibitors to relax smooth muscle tissues throughout the body, including the smooth muscle tissue of the urogenital system because PDE V is found in smooth muscle tissue in the human urogenital system, as a pharmacological alternative to other treatments and methods for prevention associated with the disorder or symptoms to be treated, (b) the nature of the problem (e.g. relaxation of smooth muscle tissue associated with BPH as a method of treatment and the known biological pathway to achieve relaxation of smooth muscle tissue, (c) the general knowledge of a person having ordinary skill in the art, and (d) various market forces driving the investigation and development of medical treatment alternatives to surgery, i.e., transurethral resection of the prostate. In addition, the patented invention is no more

than the predictable use of prior art elements with each performing the same function it had been known to perform.

3. Patents and Published Patent Applications Under 35 U.S.C. §§ 102(a)-(b), (e)

Exhibits A-19, A-23, A-24, A-26, A-29, A-30, A-31, A-33, A-35, A-36, A-37, A-50, A-53, A-55, and A-56 include charts directed to each of the following prior art patents, which are identified below by patent number, country of origin, date of issue, and first named inventor.

Exhibit	***Short Name***	***Patent / Application Number***	***Country of Origin***	***Date of Issuance / Publication***
A-19	Heiker '238	5,721,238 to Heiker et al.	United States	January 11, 1996 (filed) February 24, 1998 (issued)
A-23	March '217	5,171,217 to March et al.	United States	February 28, 1991 (filed) December 15, 1992 (issued)
A-24	Matsuura '499	94/12499 to Matsuura et al.	PCT	December 1, 1992 (filed) June 9, 1994 (published)
A-26	Morioka '962	2,084,962 to Morioka et al.	Canada	December 9, 1992 (filed) June 11, 1993 (published)
A-29	Niewohner '396	5,861,396 to Niewohner et al.	United States	October 30, 1996 (filed) January 19, 1999 (issued)
A-30	Niewohner '404	5,861,404 to Niewohner et al.	United States	January 12, 1996 (filed) January 19, 1999 (issued)
A-31	Oku '379	96/32379 to Oku et al.	PCT	April 2, 1996 (filed) October 17, 1996 (published)
A-33	Ozaki '097	95/18097 to Ozaki et al.	PCT	December 27, 1994 (filed) July 6, 1995 (published)

Exhibit	*Short Name*	*Patent / Application Number*	*Country of Origin*	*Date of Issuance / Publication*
A-35	Piazza ’666	6,207,666 to Piazza et al.	United States	April 23, 1998 (filed) March 27, 2001 (issued) June 7, 1995 (priority)
A-36	Piazza ’694	5,858,694 to Piazza et al.	United States	May 30, 1997 (filed) January 12, 1999 (issued)
A-37	Piazza ’980	6,200,980 to Piazza et al.	United States	April 17, 1997 (filed) March 13, 2001 (issued) June 7, 1995 (priority)
A-50	Sung '895	5,439,895 to Sung et al.	United States	November 19, 1993 (filed) August 8, 1995 (issued)
A-53	Takayama ’984	2,197,984 to Takayama et al.	Canada	August 29, 1995 (filed) March 7, 1996 (published)
A-55	Truss '642	195 40 642 to Truss et al.	Germany	November 1, 1995 (filed) May 7, 1997 (published)
A-56	Yoshitaka ’214	07-188214A to Yoshitaka et al.	Japan	December 24, 1993 (filed) July 25, 1995 (issued)

4. Other Publications, Uses, or Products Under 35 U.S.C. §§ 102(a)-(b)

Exhibits A-01, A-02, A-03, A-04, A-05, A-06, A-07, A-08, A-10, A-11, A-12, A-13, A-14, A-15, A-16, A-17, A-20, A-21, A-22, A-25, A-27, A-28, A-34, A-38, A-40, A-41, A-42, A-43, A-44, A-45, A-46, A-47, A-49, A-51, A-52, A-54, and A-57 include charts directed to each of the following prior art publications, which are identified below by title, date of publication, and where feasible, author and/or publisher. Exhibits A-09, A-18, A-32, A-39, and A-48 include charts directed to prior uses or products.

Exhibit	***Short Name***	**Title**	**Author/Publisher**	**Date of Publication**
A-01	Andersson	Nitric oxide synthase and nitric oxide-mediated effects in lower urinary tract smooth muscles	Andersson, K-E., et al. World journal of urology 12.5 (1994): 274-280.	October 1994
A-02	Andriole	Use of quinolones in treatment of prostatitis and lower urinary tract infections	Andriole, V. T. European Journal of Clinical Microbiology and Infectious Diseases 10.4 (1991): 342-350.	April 01, 1991
A-03	Ballard	In vitro profile of UK-92,480, an inhibitor of cyclic GMP-specific phosphodiesterase 5 for the treatment of male erectile dysfunction	Ballard, S. A., et al. J. Urol 155 (1996): 676A.	May 1996
A-04	Barbier	Relaxant influence of phosphodiesterase inhibitors in the cat gastric fundus	Barbier, Ann J., et al. European journal of pharmacology 276.1 (1995): 41-47.	March 24, 1995
A-05	Boolell	Sildenafil: an orally active type 5 cyclic GMP-specific phosphodiesterase inhibitor for the treatment of penile erectile dysfunction.	Boolell, Mitradev, et al. International journal of impotence research 8.2 (1996): 47-52.	June 1, 1996
A-06	Boolell 2	Sildenafil, a novel effective oral therapy for male erectile dysfunction	Boolell, M., et al. British journal of urology 78.2 (1996): 257-261.	August 1, 1996
A-07	Burnett	Nitric oxide control of lower genitourinary tract functions: a review	Burnett, Arthur L., Urology 45.6 (1995): 1071-1083	June 1995
A-08	Burnett 2	Nitric oxide control of lower genitourinary tract functions: a review	Burnett, Arthur L., et al. Urology 45.6 (1995): 1071-1083.	June 1, 1995
A-09	Caffeine			
A-10	Caine	Antispasmodic effects of flavoxate, MFCA, and REC 15/2053 on smooth muscle of human prostate and urinary bladder	Caine, M., et al., Urology 37.4 (1991): 390-394	April 1991
A-11	Champault	A double-blind trial of an extract of the plant Serenoa repens in benign prostatic hyperplasia	Champault, G., et al. British journal of clinical pharmacology 18.3 (1984): 461-462.	September 1, 1984
A-12	Coste	Characterization of a novel	Coste, Hervé, et al.	November 9, 1995

Exhibit	*Short Name*	Title	Author/Publisher	Date of Publication
		potent and specific inhibitor of type V phosphodiesterase	Biochemical pharmacology 50.10 (1995): 1577-1585.	
A-13	Czarniecki	Inhibitors of types I and V phosphodiesterase: Elevation of cGMP as a therapeutic strategy	Czarniecki, Michael, et al. Annual reports in medicinal chemistry 31 (1996): 61-70.	October 14, 1996
A-14	Di Silverio	Plant extracts in BPH	Di Silverio, F., et al. Minerva urologica e nefrologica= The Italian journal of urology and nephrology 45.4 (1993): 143-149.	December 1, 1993
A-15	Dokita	N G-nitro-L-arginine inhibits non-adrenergic, non-cholinergic relaxation in rabbit urethral smooth muscle	Dokita, Shinobu, et al. Life sciences 48.25 (1991): 2429-2436.	January 1, 1991
A-16	Drescher	Alpha-1 receptor mediated smooth muscle regulation in benign prostatic hyperplasia	Drescher, P., et al., Scandinavian journal of urology and nephrology. Supplementum 157 (1993): 33-40	January 1994
A-17	Drescher 2	Smooth muscle contractility in prostatic hyperplasia: role of cyclic adenosine monophosphate	Drescher, P., et al., The Prostate 25.2 (1994): 76-80	August 08, 1994
A-18	Epimedium Herbs			
A-20	Ishigooka	Clinical and retrospective evaluation of Eviprostat: A non-hormonal and non-neuropharmacological agent for benign prostatic hyperplasia	Ishigooka, M., et al. International urology and nephrology 27.1 (1995): 61-66.	January 01, 1995
A-21	Lepor 3	Medical therapy for benign prostatic hyperplasia	Lepor, Herbert Urology 42.5 (1993): 483-501.	January 12, 1995
A-22	Lowe 2	Phytotherapy in treatment of benign prostatic hyperplasia: a critical review	Lowe, Franklin C., et al. Urology 48.1 (1996): 12-20.	July 01, 1996
A-25	Monda	Medical treatment of benign	Monda, Jeffrey M., et al.	July 1, 1993

Exhibit	*Short Name*	Title	Author/Publisher	Date of Publication
		prostatic hyperplasia: 5α-reductase inhibitors and α-adrenergic antagonists	Mayo Clinic proceedings. Vol. 68. No. 7. Elsevier, 1993.	
A-27	Murray 2	Phosphodiesterase VA Inhibitors	Murray, Kenneth J. Drug News and Perspectives 6 (1993): 150-156.	June 1, 1993
A-28	Narayan	Pharmacotherapy for benign prostatic hyperplasia	Narayan, Perinchery, et al. Western journal of medicine 161.5 (1994): 495.	November 1, 1994
A-32	Onion			
A-34	Persson	Non-adrenergic, non-cholinergic relaxation and levels of cyclic nucleotides in rabbit lower urinary tract	Persson, Katarina, et al. European Journal of Pharmacology: Molecular Pharmacology 268.2 (1994): 159-167.	July 1, 1994
A-38	Plosker	Serenoa repens (Permixon®)	Plosker, Greg L., et al. Drugs & aging 9.5 (1996): 379-395.	November 1, 1996
A-39	Pomegranate Juice			
A-40	Rajfer	Nitric oxide as a mediator of relaxation of the corpus cavernosum in response to nonadrenergic, noncholinergic neurotransmission	Rajfer, Jacob, et al. New England Journal of Medicine 326.2 (1992): 90-94.	January 9, 1992
A-41	Red Wine			
A-42	Rickards	Benign prostatic hyperplasia: A Colour Guide	Rickards, D., et al. (1994). Graftham Press..	January 1, 1994
A-43	Roylance	Current treatment of BPH	Roylance, P., et al. Biomedicine & pharmacotherapy 49.7 (1995): 332-338.	January 1, 1995
A-44	Ruffmann	A review of flavoxate hydrochloride in the treatment of urge incontinence	Ruffmann, R., Journal of international medical research 16.5 (1988): 317-330	October 1988
A-45	Ruutu	Efficacy and side-effects of prazosin as a symptomatic treatment of benign	Ruutu, Mirja L., et al. Scandinavian journal of urology and nephrology	January 1, 1990

Exhibit	***Short Name***	**Title**	**Author/Publisher**	**Date of Publication**
		prostatic obstruction	25.1 (1991): 15-19.	
A-46	Saeki	A selective type V phosphodiesterase inhibitor, E4021, dilates porcine large coronary artery	Saeki, Takao, et al. Journal of Pharmacology and Experimental Therapeutics 272.2 (1995): 825-831.	February 1, 1995
A-47	Schudt	Phosphodiesterase Inhibitors	Schudt, C., et al. (1996). Academic Press.	August 27, 1996
A-48	Serenoa Repens			
A-49	Shahid	Comparison of cyclic nucleotide phosphodiesterase isoenzymes in rat and rabbit ventricular myocardium: positive inotropic and phosphodiesterase inhibitory effects of Org 30029, milrinone and rolipram	Shahid, M., et al. Naunyn-Schmiedeberg's archives of pharmacology 342.6 (1990): 698-705.	December 01, 1990
A-51	Sybertz	cGMP phosphodiesterase inhibition: A new mechanism for the discovery of therapeutic agents	Sybertz, E. J., et al. Current Pharma. Design 1.4 (1995): 373-390.	December 1, 1995
A-52	Taher	Characterization of cyclic nucleotide phosphodiesterase isoenzymes in the human ureter and their functional role in vitro	Taher, A., et al. World journal of urology 12.5 (1994): 286-291.	October 31, 1994
A-54	Takeda	Effects of nitric oxide on human and canine prostates	Takeda, Masayuki, et al. Urology 45.3 (1995): 440-446.	March 1, 1995
A-57	Cheung	TCM Management: Benign Prostate Hyperplasia (Long Bi-Prostatism)	Cheung, C.S. and Deaton, K., Harmonious Sunshine Cultural Center	1994

To the extent any limitation is construed to have a similar meaning, or to encompass similar feature(s) and/or function(s), with any other claim limitation, and to the extent at least one claim chart in Exhibits A-1 through A-57 hereto identifies any prior art reference as

disclosing or teaching such similarly construed claim limitation, such identified prior art reference and Defendants' contentions with respect to same, are incorporated by reference.

Defendants reserve the right to rely upon (1) foreign counterparts of the U.S. Patents identified in Defendants' Invalidity Contentions, (2) U.S. counterparts of foreign patents and foreign patent applications identified in Defendants' Invalidity Contentions, and (3) U.S. and foreign patents and patent applications corresponding to articles and publications identified in Defendants' Invalidity Contentions. The claim charts of exhibits identified in Section 5 below indicate disclosures within the prior art references that teach or suggest each and every element of the asserted claims. To the extent that an element of an Asserted Claim is not found in a chart, the claim is rendered obvious by the references charted, modification of the references in light of the knowledge of one of ordinary skill in the art, and/or in combination with one or more other prior art references as discussed below in Section 6. Each reference or combination of references suggested by these charts in Exhibits A-1 through A-57 provide notice of whether the prior art renders the claim obvious or anticipated pursuant to P.R. 3-3(b).

5. Prior Art References, Products, or Uses that Anticipate the Asserted Claims

Defendants contend that the Accused Claims are anticipated either expressly or inherently based on the following prior art references, products, or uses:

Exhibit	***Short Name***	***Title / Patent / Application Number***	***Author/Publisher / Country of Origin***	***Date of Issuance / Publication***
A-02	Andriole	Use of quinolones in treatment of prostatitis and lower urinary tract infections	Andriole, V. T. European Journal of Clinical Microbiology and Infectious Diseases 10.4 (1991): 342-350.	April 01, 1991
A-09	Caffeine			
A-11	Champault	A double-blind trial of an extract of the plant Serenoa repens in benign	Champault, G., et al. British journal of clinical pharmacology	September 1, 1984

Exhibit	*Short Name*	*Title / Patent / Application Number*	*Author/Publisher / Country of Origin*	*Date of Issuance / Publication*
		prostatic hyperplasia	18.3 (1984): 461-462.	
A-14	Di Silverio	Plant extracts in BPH	Di Silverio, F., et al. Minerva urologica e nefrologica= The Italian journal of urology and nephrology 45.4 (1993): 143-149.	December 1, 1993
A-15	Dokita	N G-nitro-L-arginine inhibits non-adrenergic, non-cholinergic relaxation in rabbit urethral smooth muscle	Dokita, Shinobu, et al. Life sciences 48.25 (1991): 2429-2436.	January 1, 1991
A-16	Drescher	Alpha-1 receptor mediated smooth muscle regulation in benign prostatic hyperplasia	Drescher, P., et al., Scandinavian journal of urology and nephrology. Supplementum 157 (1993): 33-40	January 1994
A-17	Drescher 2	Smooth muscle contractility in prostatic hyperplasia: role of cyclic adenosine monophosphate	Drescher, P., et al., The Prostate 25.2 (1994): 76-80	August 08, 1994
A-18	Epimedium Herbs			
A-19	Heiker ’238	5,721,238 to Heiker et al.	United States	January 11, 1996 (filed) February 24, 1998 (issued)
A-20	Ishigooka	Clinical and retrospective evaluation of Eviprostat: A non-hormonal and non-neuropharmacological agent for benign prostatic hyperplasia	Ishigooka, M., et al. International urology and nephrology 27.1 (1995): 61-66.	January 01, 1995
A-22	Lowe 2	Phytotherapy in treatment of benign prostatic hyperplasia: a critical review	Lowe, Franklin C., et al. Urology 48.1 (1996): 12-20.	July 01, 1996
A-23	March ’217	5,171,217 to March et al.	United States	February 28, 1991 (filed) December 15, 1992 (issued)
A-24	Matsuura ’499	94/12499 to Matsuura et al.	PCT	December 1, 1992 (filed)

Exhibit	*Short Name*	*Title / Patent / Application Number*	*Author/Publisher / Country of Origin*	*Date of Issuance / Publication*
				June 9, 1994 (published)
A-26	Morioka ’962	2,084,962 to Morioka et al.	Canada	December 9, 1992 (filed) June 11, 1993 (published)
A-29	Niewohner ’396	5,861,396 to Niewohner et al.	United States	October 30, 1996 (filed) January 19, 1999 (issued)
A-30	Niewohner ’404	5,861,404 to Niewohner et al.	United States	January 12, 1996 (filed) January 19, 1999 (issued)
A-31	Oku ’379	96/32379 to Oku et al.	PCT	April 2, 1996 (filed) October 17, 1996 (published)
A-32	Onion			
A-37	Piazza ’980	6,200,980 to Piazza et al.	United States	April 17, 1997 (filed) March 13, 2001 (issued) June 7, 1995 (priority)
A-38	Plosker	Serenoa repens (Permixon®)	Plosker, Greg L., et al. Drugs & aging 9.5 (1996): 379-395.	November 1, 1996
A-39	Pomegranate Juice			
A-42	Rickards	Benign prostatic hyperplasia: A Colour Guide	Rickards, D., et al. (1994). Graftham Press..	January 1, 1994
A-43	Roylance	Current treatment of BPH	Roylance, P., et al. Biomedicine & pharmacotherapy 49.7 (1995): 332-338.	January 1, 1995
A-44	Ruffmann	A review of flavoxate hydrochloride in the treatment of urge incontinence	Ruffmann, R., Journal of international medical research 16.5 (1988): 317-330	October 1988
A-48	Serenoa Repens			
A-50	Sung '895	5,439,895 to Sung et al.	United States	November 19, 1993 (filed)

Exhibit	*Short Name*	*Title / Patent / Application Number*	*Author/Publisher / Country of Origin*	*Date of Issuance / Publication*
				August 8, 1995 (issued)
A-53	Takayama ’984	2,197,984 to Takayama et al.	Canada	August 29, 1995 (filed) March 7, 1996 (published)
A-55	Truss '642	195 40 642 to Truss et al.	Germany	November 1, 1995 (filed) May 7, 1997 (published)
A-56	Yoshitaka ’214	07-188214A to Yoshitaka et al.	Japan	December 24, 1993 (filed) July 25, 1995 (issued)
A-57	Cheung	TCM Management: Benign Prostate Hyperplasia (Long Bi-Prostatism)	Cheung, C.S. and Deaton, K., Harmonious Sunshine Cultural Center	1994

As even a cursory review of the identified charts makes clear, the prior art is replete with references, products, and uses which teach the use of PDE V inhibitors for the prevention and treatment of BPH. Moreover, the prior art teaches the use of various natural products, *e.g.* red wine, caffeine, onions, garlic, Permixon® (saw palmetto extract) and others, to prevent and treat BPH. These natural products contain key active ingredients which have been demonstrated to inhibit PDE V. Evidence of the PDE V inhibitory nature of the active ingredient in any such natural product is identified in connection with any such prior art. Further, phytotherapy, the use of plants or plant extracts for medicinal uses, has been described or used since ancient times as effective for the treatment of symptoms of BPH and other urogenital diseases. In addition, it is clear that Chinese herbal medications have been used for more than a hundred years to treat the symptoms of BPH. These medications contain key active ingredients which have been shown to inhibit PDE V. Thus, the prior public uses of such herbal medications, natural products, and

plant extracts, and the prior art teachings of the same, inherently disclose the use of PDE V inhibitors for the treatment and prevention of BPH.

As noted, certain pieces of identified prior art inherently disclose features of the Asserted Claims. Defendants reserve the right to rely on inherency to demonstrate the invalidity of the Asserted Claims. Defendants may rely on any evidence, including expert testimony, to establish the inherency of certain features of the prior art to invalidate the Asserted Claims. Defendants also reserve the right to rely on any evidence, including expert testimony, to prove that the solutions or prior art cited herein are enabled or to explain the meaning of a term used in the solutions or any prior art cited herein.

6. Prior Art that Renders the Asserted Claims Obvious

Based upon the teachings of the references provided herewith, and application of ordinary skill in the art, it would have been obvious to a person of ordinary skill in the art to administer an effective amount of an inhibitor of PDE V to a person in need of prophylaxis or treatment of BPH. The claimed elements were known in the prior art, and one skilled in the art could have combined the claimed elements using known methods to yield reasonably predictable results. The relaxation of the lower urinary tract smooth muscle, including that of the prostate, was a known and recognized therapeutic target for the prophylaxis or treatment of BPH at the time of the invention. There were a finite number of ways known at the time of the invention to relax smooth muscle in the urogenital systems, including prostatic smooth muscle. The mechanism of action of inhibitors of PDE V to relax smooth muscle was known and recognized at the time of the invention. It would have been obvious to try inhibitors of PDE V to achieve a reasonably predictable result of relaxation of lower urinary tract smooth muscle, including that of the prostate, with a reasonable expectation of success for the prophylaxis or treatment of BPH. A person of ordinary skill in the art would have been motivated by that person's own knowledge,

the teachings and suggestions in this reference and other references provided herewith, and market forces (such as the need for medical, non-invasive and less expensive treatments for condition affecting a large portion of the male population), to combine and use the known mechanism of action of PDE V inhibitors to induce known and reasonably predictable therapeutic objectives for the prophylaxis or treatment of BPH to arrive at the claimed invention of the '124 Patent.

For the sake of efficiency, it is noted that several of the prior art references identified in this document contain similar or cumulative teachings, and will therefore be grouped together in the sections below for ease of reference in the accompanying charts. The categorization or description of a reference is not an admission that the reference does not disclose, teach, or suggest elements or features related to a different category. Defendants also rely on combinations of references disclosed herein that are not explicitly made part of the below groups, as well as combinations of references from the same group.

a) Prophylaxis or Treatment of BPH

One of skill in the art would know the high prevalence of the development of BPH in aging males. "Benign prostatic hyperplasia (BPH), as the most common benign neoplasm in the aging human male, has a high prevalence that increases progressively with age. The prevalence of histologically identifiable BPH for 60-year-old males is greater than 50 percent. By age 85, the prevalence is approximately 90 percent."

> It is so common in the aging male that it could be considered a normal and predictable part of the ageing process. Although not all males with BPH have sufficiently severe symptoms to warrant surgical intervention, it has become apparent that there are large numbers of men with mild but gradually worsening symptoms who do not currently seek treatment for the condition.
>
> Furthermore, it is anticipated that demographic changes in the population, particularly in Western countries, will lead to an increase in the numbers of elderly males and hence more patients will present with symptoms in the future. A

> fear of surgery and the potential risks and complications of surgery have combined to inspire an interest in alternative treatments for BPH.

See D. Rickards and T.J. Christmas, "Benign Prostatic Hyperplasia: A Colour Guide" (1994) Graffman Press Ltd.

> An estimated one in every four men in the United States will be treated for the relief of symptomatic BPH by age 80 (Barry, 1990, 1991). Over 300,000 surgical procedures for BPH, mostly transurethral resection of the prostate (TURP) are performed annually in the United States (Holtgrewe, Mebust, Dowd, et al., 1989). TURP is the second most common surgical procedure performed in the Medicare population, second only to cataract surgery. The resulting related cost is estimated to be in excess of $2 billion per year (Holtgrewe, Mebust, Dowd, et al., 1989).

Benign Prostatic Hyperplasia: Diagnosis and Treatment, Clinical Practice Guideline, No. 8, U.S. Department of Health and Human Services, AHCPR Publication No. 94-0582, February 1994.

For example, the importance of medical treatments in lieu of the surgical option (transurethral resection of the prostate, or TURP) for several reasons, including the expense, the associated morbidity, and reduced life expectancy, was disclosed as follows:

> Because of these concerns [with transurethral resection of the prostate], interest in the development of medical therapies for the management of symptomatic BPH has flourished in recent years. This activity has been fueled by (1) the medical community's quest to develop an alternative treatment for such a common condition, (2) the inordinate cost associated with the current surgical approach, (3) the federal government's attempt to control health-care costs, and (4) the patient's desire to avoid surgical treatment and its associated risks. Because of the high prevalence of BPH in our aging population, feasible, low-risk, effective and cost-efficient options are necessary. Clearly, the 1990s represents a transition period during which the management of symptomatic BPH is more more medical and less surgical.

Jeffrey M. Monda and Joseph E. Oesterling, "Medical Treatment of Benign Prostatic Hyperplasia: 5α-Reductase Inhibitors and α-Adrenergic Antagonists," Mayo Clin Proc 1993; 68:670-679, at p. 671. Thus, there existed motivation to persons skilled in the art to apply other medical treatments known to relax smooth muscle, including in the lower urinary tract (such as PDE V inhibitors) to treat BPH.

The prior art discloses the symptoms and treatment of BPH as well as the known physiological pathways involved in the symptoms of BPH and the motivation to seek medical treatment in lieu of surgery. The prior art shows that one of ordinary skill in the art would know that the urogenital system, including the prostate gland and other tissues, are composed of a large amount of smooth muscle tissue that, if relaxed, would alleviate, prevent, or treat symptoms of BPH.

b) Inhibitors of Phosphodiesterase (PDE) V

The prior art discloses the identity of PDE V, its role in the management of the intracellular concentration of cGMP; its location in the various smooth muscle tissue of the body including the urogenital system; and the impact on smooth muscle tissue (i.e., relaxation) when PDE V is inhibited—i.e., that smooth muscle tissue will be relaxed via increase in the intracellular concentration of cGMP; that the concentration of cGMP can be controlled by the presence of PDE V; and that the increase in cGMP concentration could occur via various mechanisms including the inhibition of PDE V. *See, e.g.*, Paul J. Silver, "Inhibition of Phosphodiesterase Isoenzymes and Cell Function by Selective PDE5 Inhibitors," *Phosphodiesterase Inhibitors*, ed. Christian Schudt, Gordon Dent and Klaus F. Rabe, Academic Press, Harcourt Brace and Company (1996). Further, the prior art shows that the inhibition of PDE V, with an effective amount of an inhibitor of PDE V, was a known pharmacological treatment or prophylactic for various diseases and disorders (including those of the urogenital system) to achieve relaxation of various smooth muscle tissue, including in the urogenital system.

Given the prevalence of the disease in a substantial portion of the male population, and the costs, risks, and personal fears associated with surgical treatment of BPH, there existed significant market forces at the time of the alleged invention of the '124 Patent to seek less

expensive, non-invasive medical treatments for BPH. One of skill in the art would have been motivated to substitute PDE V inhibitors for other agents, such as alpha-blockers and PDE IV inhibitors already being used achieve smooth muscle relaxation to treat BPH, in order to reach the claimed invention.

c) Dosage and Administration of Pharmacological Treatments

The prior art discloses the administration of PDE V inhibitors in pharmacologically acceptable excipient forms administered in a unit dose form. Moreover, the use of compounds, such as those disclosed in the foregoing references, in combination with a pharmacologically acceptable excipient administered in a unit dose form would be obvious to, and within the routine, conventional knowledge and experience, of a person of ordinary skill in the art. *See*, *e.g.*, The Merck Index: An Encyclopedia of Chemicals, Drugs and Biologicals, 12th edition (1996); *see also* Remington: The Science and Practice of Pharmacy, 19th edition (1995).

d) Obviousness Combinations

It would have been obvious to a person of skill in the art to have taken the teachings, disclosures, and knowledge of the prophylaxis or treatment of BPH, as reflected in the prior art, and combine that with the teachings, disclosures, and knowledge of inhibitors of PDE V, as reflected in the prior art, to reach the purported invention of the Asserted Claims of the ‘124 Patent. Specifically:

Burnett teaches the prophylaxis or treatment of BPH, and in combination with the teachings, disclosures, and knowledge persons of skill in the art of inhibitors of PDE V, as reflected in any of the following references, Ozaki 997, Sybertz, Murray 2, Schudt, Persson, Ballard, Barbier, Piazza '694, Boolell, Boolell 2, Coste, Czarniecki, Saeki, Piazza ‘666, renders the obvious the purported invention of the Asserted Claims of the ‘124 Patent.

Burnett 2 teaches the prophylaxis or treatment of BPH, and in combination with the teachings, disclosures, and knowledge persons of skill in the art of inhibitors of PDE V, as reflected in any of the following references, Ozaki 997, Sybertz, Murray 2, Schudt, Persson, Ballard, Barbier, Piazza '694, Boolell, Boolell 2, Coste, Czarniecki, Saeki, Piazza ‘666, renders the obvious the purported invention of the Asserted Claims of the ‘124 Patent.

Caine teaches the prophylaxis or treatment of BPH, and in combination with the teachings, disclosures, and knowledge persons of skill in the art of inhibitors of PDE V, as reflected in any of the following references, Ozaki 997, Sybertz, Murray 2, Schudt, Persson, Ballard, Barbier, Piazza '694, Boolell, Boolell 2, Coste, Czarniecki, Saeki, Piazza ‘666, renders the obvious the purported invention of the Asserted Claims of the ‘124 Patent.

Drescher teaches the prophylaxis or treatment of BPH, and in combination with the teachings, disclosures, and knowledge persons of skill in the art of inhibitors of PDE V, as reflected in any of the following references, Ozaki 997, Sybertz, Murray 2, Schudt, Persson, Ballard, Barbier, Piazza '694, Boolell, Boolell 2, Coste, Czarniecki, Saeki, Piazza ‘666, renders the obvious the purported invention of the Asserted Claims of the ‘124 Patent.

Drescher 2 teaches the prophylaxis or treatment of BPH, and in combination with the teachings, disclosures, and knowledge persons of skill in the art of inhibitors of PDE V, as reflected in any of the following references, Ozaki 997, Sybertz, Murray 2, Schudt, Persson, Ballard, Barbier, Piazza '694, Boolell, Boolell 2, Coste, Czarniecki, Saeki, Piazza ‘666, renders the obvious the purported invention of the Asserted Claims of the ‘124 Patent.

Lepor 3 teaches the prophylaxis or treatment of BPH, and in combination with the teachings, disclosures, and knowledge persons of skill in the art of inhibitors of PDE V, as reflected in any of the following references, Ozaki 997, Sybertz, Murray 2, Schudt, Persson,

Ballard, Barbier, Piazza '694, Boolell, Boolell 2, Coste, Czarniecki, Saeki, Piazza ‘666, renders the obvious the purported invention of the Asserted Claims of the ‘124 Patent.

Monda teaches the prophylaxis or treatment of BPH, and in combination with the teachings, disclosures, and knowledge persons of skill in the art of inhibitors of PDE V, as reflected in any of the following references, Ozaki 997, Sybertz, Murray 2, Schudt, Persson, Ballard, Barbier, Piazza '694, Boolell, Boolell 2, Coste, Czarniecki, Saeki, Piazza ‘666, renders the obvious the purported invention of the Asserted Claims of the ‘124 Patent.

Takeda teaches the prophylaxis or treatment of BPH, and in combination with the teachings, disclosures, and knowledge persons of skill in the art of inhibitors of PDE V, as reflected in any of the following references, Ozaki 997, Sybertz, Murray 2, Schudt, Persson, Ballard, Barbier, Piazza '694, Boolell, Boolell 2, Coste, Czarniecki, Saeki, Piazza ‘666, renders the obvious the purported invention of the Asserted Claims of the ‘124 Patent.

Narayan teaches the prophylaxis or treatment of BPH, and in combination with the teachings, disclosures, and knowledge persons of skill in the art of inhibitors of PDE V, as reflected in any of the following references, Ozaki 997, Sybertz, Murray 2, Schudt, Persson, Ballard, Barbier, Piazza '694, Boolell, Boolell 2, Coste, Czarniecki, Saeki, Piazza ‘666, renders the obvious the purported invention of the Asserted Claims of the ‘124 Patent.

Rajfer teaches the prophylaxis or treatment of BPH, and in combination with the teachings, disclosures, and knowledge persons of skill in the art of inhibitors of PDE V, as reflected in any of the following references, Ozaki 997, Sybertz, Murray 2, Schudt, Persson, Ballard, Barbier, Piazza '694, Boolell, Boolell 2, Coste, Czarniecki, Saeki, Piazza ‘666, renders the obvious the purported invention of the Asserted Claims of the ‘124 Patent.

Roylance teaches the prophylaxis or treatment of BPH, and in combination with the teachings, disclosures, and knowledge persons of skill in the art of inhibitors of PDE V, as reflected in any of the following references, Ozaki 997, Sybertz, Murray 2, Schudt, Persson, Ballard, Barbier, Piazza '694, Boolell, Boolell 2, Coste, Czarniecki, Saeki, Piazza ‘666, renders the obvious the purported invention of the Asserted Claims of the ‘124 Patent.

Ruffman teaches the prophylaxis or treatment of BPH, and in combination with the teachings, disclosures, and knowledge persons of skill in the art of inhibitors of PDE V, as reflected in any of the following references, Ozaki 997, Sybertz, Murray 2, Schudt, Persson, Ballard, Barbier, Piazza '694, Boolell, Boolell 2, Coste, Czarniecki, Saeki, Piazza ‘666, renders the obvious the purported invention of the Asserted Claims of the ‘124 Patent.

Ruutu teaches the prophylaxis or treatment of BPH, and in combination with the teachings, disclosures, and knowledge persons of skill in the art of inhibitors of PDE V, as reflected in any of the following references, Ozaki 997, Sybertz, Murray 2, Schudt, Persson, Ballard, Barbier, Piazza '694, Boolell, Boolell 2, Coste, Czarniecki, Saeki, Piazza ‘666, renders the obvious the purported invention of the Asserted Claims of the ‘124 Patent.

Based upon the teachings of these references, and application of ordinary skill, knowledge, and experience in the art, it would have been obvious to a person of ordinary skill in the art to administer an effective amount of a pharmacological inhibitor of PDE V to a person in need of prophylaxis or treatment of BPH. The claimed elements were known in the prior art, and one skilled in the art could have combined the claimed elements using known methods to yield reasonably predictable results. The relaxation of the lower urinary tract smooth muscle, including that of the prostate, was a known and recognized therapeutic target for the prophylaxis or treatment of BPH at the time of the invention. There were a finite number of ways known at the

time of the invention to pharmacologically relax lower urinary tract smooth muscle, including that of the prostate. The mechanism of action of inhibitors of PDE V to relax smooth muscle was known and recognized at the time of the invention. It would have been obvious to try pharmacological inhibitors of PDE V to achieve a reasonably predictable result of relaxation of lower urinary tract smooth muscle, including that of the prostate, with a reasonable expectation of success for the prophylaxis or treatment of BPH. A person of ordinary skill in the art would have been motivated by that person's own knowledge, the teachings and suggestions in this reference and other references provided herewith, and market forces (such as the need for medical, non-invasive and less expensive treatments for condition affecting a large portion of the male population), to combine and use the known mechanism of action of PDE V inhibitors to induce known and reasonably predictable therapeutic objectives for the prophylaxis or treatment of BPH to arrive at the claimed invention of the '124 Patent.

In addition, one of ordinary skill in the art would have been motivated to combine the prior art references identified above to solve at least the same problems ostensibly addressed by the '124 Patent. For example, the known mechanism of action of relaxation of smooth muscle cells through medical treatment as a treatment for BPH had been addressed in various ways, e.g., through pharmacological agents as well as natural products. In addition, the known mechanism of action of relaxation of smooth muscle cells by inhibition of PDE V had been addressed in various tissues (including various genitourinary tissues) for various therapeutic objectives. It would have been obvious to one of ordinary skill in the art to have combined the references showing the known ways of inducing smooth muscle relaxation to treat BPH with references demonstrating the known use of inhibitors of PDE V, both pharmacological and natural, to

induce smooth muscle relaxation in various human cells, including within the genitourinary system (which includes the prostate).

One of ordinary skill in the art would have been motivated to combine each of the prior art references identified in Exhibit A in a manner that would render obvious the Asserted Claims of the '124 Patent. As the Supreme Court held in *KSR Int'l Co. v. Teleflex, Inc.*, "[t]he combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." 127 U.S. 1727, 1731 (2007). "When a work is available in one field of endeavor, design incentives and other market forces can prompt variations of it, either in the same field or a different one. If a person of ordinary skill can implement a predictable variation, § 103 likely bars its patentability." *Id.* at 1740. Accordingly, a person of skill in the art would have been motivated to combine or adapt known or familiar methods in the art, especially where market forces prompt such variations. Here, market forces demanded non-surgical, non-invasive, medical treatments or prevention means for BPH which the patent states affects at least 50% of all men fifty years and older (and persons of skill in the art would know the incidence of BPH with men increases with age, i.e., more than 90% of men over the age of 85 affected with BPH). Thus, one of skill in the art would have thought to combine or modify references that described known methods which one of skill in the art would have recognized as offering improvements to existing treatments of BPH.

The references in Exhibit A describe, incorporate or implement pharmacological, other medicinal, and natural treatments that were known to offer such improvements; accordingly, one of skill in the art would have been motivated to combine or modify the references in a manner that renders obvious the Asserted Claims. Moreover, the Supreme Court held that "familiar items may have obvious uses beyond their primary purposes, and in many cases a person of ordinary

skill will be able to fit the teachings of multiple patents together like pieces of a puzzle." *Id.* at 1742. Indeed, it is sufficient that a combination of elements was "obvious to try." *Id.* ("When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp."). Motivation to combine may also be found in the "nature of the problem." *Id*. at 1734.

Here, the need to prevent or treat BPH in a large and growing population of men would have led one of skill in the art to combine the known mechanism of action of relaxing smooth muscle in the prostate or elsewhere in the genitourinary system with known pharmacological or natural means known to relax smooth muscle of many other human tissues. Accordingly, the teaching, suggestion, or motivation to modify or combine references in the manner claimed can be found in the explicit and/or implicit teachings of the references and prior art as a whole, the general knowledge of those skilled in the art, including knowledge of trends in the field, and knowledge that art is of special interest or importance in the field. The references set forth in Exhibit A demonstrate that there were, at the time of the alleged invention, a finite number of predictable solutions to induce smooth muscle relaxation for medically preventing or treating BPH.

These are only examples of the teachings, suggestions, motivations and/or reasons a person of ordinary skill in the art would have had to modify or combine the prior art noted in the charts included in Exhibit A. Such teachings, suggestions, motivations, and/or reasons are also further identified in Exhibit A charts with reference to disclosure of particular limitations. The Exhibit A charts describe example points in the prior art references at which a particular aspect of the claims are taught. Each of these teachings noted in the Exhibit A charts would teach,

suggest, motivate, and/or provide a reason to a person of ordinary skill the art to modify or combine prior art references in relation to the treatment and prevention of BPH using PDE inhibitors. For these reasons and others, a person of ordinary skill in the art would have been motivated to combine any one of the prior art references listed in the Exhibit A charts with one or more of those prior art references listed in Exhibit A.

Thus, the Defendants identify the foregoing combinations of items of prior art that make each Asserted Claim obvious. The charts included in Exhibit A show examples of where elements of each Asserted Claim are found in each noted item of prior art. In addition, to the extent any element of the Asserted Claims is not found in one or more of the references identified above as anticipatory of the Asserted Claims, such reference may be combined with one or more other references in Exhibit A to reach the purported invention of the Asserted Claims. It would have been obvious to combine the teachings of any two or more of the references contained in the charts that generally teach the methods of treating and preventing any disorder or disease, including BPH , by use of inhibitors of PDE V in the smooth muscle tissue of the urogenital system.

In addition, as noted above, Defendants will seek discovery regarding additional prior art in the possession, custody or control of Plaintiff and third parties. This discovery is ongoing, and Defendants reserve the right to seek leave to amend their Invalidity Contentions as new information is discovered.

B. Contentions Under P.R. 3-3(d)

Pursuant to P.R. 3-3(d), Defendants list below the grounds upon which the asserted claims of the ’124 Patent are invalid based on lack of written description under 35 U.S.C § 112(1), lack of enablement under 35 U.S.C. § 112(1), indefiniteness under 35 U.S.C. § 112(2), and indefiniteness under 35 U.S.C. § 112(6). Defendants further contend that Plaintiffs’

apparent claim constructions render the Asserted Claims unsupported and well-beyond the disclosure of the '124 Patent as would be understood by one of ordinary skill in the art.

1. Invalidity Under 35 U.S.C. § 112, ¶ 1

35 U.S.C. § 112, paragraph 1, includes both an enablement and written description requirement. See 35 U.S.C. § 112(1) ("The specification shall contain a written description . . . of the manner and process of making and using [the invention] in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same.").

To satisfy the enablement requirement of 35 U.S.C. § 112, ¶ 1, the disclosure "must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *Sitrick v. Dreamworks, LLC*, 516 F.3d 993, 999 (Fed. Cir. 2008). Moreover, "'[i]t is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement." *Genentech, Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 1366 (Fed. Cir. 1997). The Federal Circuit has enumerated several factors to consider in determining whether a disclosure would require "undue experimentation": (1) the quantity of experimentation necessary; (2) the amount of direction or guidance presented; (3) the presence or absence of working examples; (4) the nature of the invention; (5) the state of the prior art; (6) the relative skill of those in the art; (7) the predictability or unpredictability of the art; and (8) the breadth of the claims. *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988).

To satisfy the written description requirement, the description must "clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed." *Ariad Pharmaceuticals, Inc. v. Eli Lilly and Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010). In other words, the test for sufficiency is whether the disclosure of the application relied upon reasonably

conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date. *Id.* The test requires an objective inquiry into the four corners of the specification from the perspective of a person of ordinary skill in the art. Based on that inquiry, the specification must describe an invention understandable to that skilled artisan and show that the inventor actually invented the invention claimed. "Whether the written description requirement is satisfied is a fact-based inquiry that will depend on the nature of the claimed invention and the knowledge of one skilled in the art at the time an invention is made and a patent application is filed." *Carnegie Mellon Univ. v. Hoffmann La Roche Inc*., 541 F.3d 1115, 1122 (Fed. Cir. 2008).

Actual "possession" or reduction to practice outside of the specification is not enough. Rather, as stated above, it is the specification itself that must demonstrate possession. And while the description requirement does not demand any particular form of disclosure, *Carnegie Mellon Univ.*, 541 F.3d at 1122, or that the specification recite the claimed invention in haec verba, a description that merely renders the invention obvious does not satisfy the requirement, *Lockwood v. Am. Airlines*, 107 F.3d 1565, 1571–72 (Fed. Cir. 1997).

Defendants contend that the Asserted Claims of the '124 Patent are invalid because they do not comply with the enablement or written description requirements of 35 U.S.C. § 112, ¶ 1.

a) Invalidity for Lack of Enablement

The '124 Patent is invalid for lack of enablement under 35 U.S.C. § 112, ¶ 1 because the specification fails to sufficiently disclose the manner of identifying, making and/or using the claimed "effective amount of an inhibitor of phosphodiesterase (PDE) V" sufficient or adequate for the prophylaxis or treatment of BPH. The specification does not teach the potency of PDE V inhibition required to make and use "an inhibitor of phosphodiesterase (PDE) V" for the treatment of BPH. For example, the specification makes no distinction, and contains no teaching,

as to the level of potency for any of the disclosed inhibitors of PDE I, PDE IV, and PDE V to be adequate to treat BPH.

A person of ordinary skill in the art would have to engage in unreasonable and undue experimentation to make and use the claimed "inhibitors of phosphodiesterase (PDE) V." Factors such as the breadth of the claim (the function of inhibiting PDE V), the nature of the invention, the state of the art, quantity of experimentation necessary to practice the full scope of the claim, the lack of working examples, and the level of unpredictability in the chemical arts, all demonstrate a lack of enablement due to undue experimentation. A person of ordinary skill in the art would have to synthesize and screen a large number of compounds to determine whether any one inhibits PDE V, without any guidance from the '124 Patent as to the potency or selectivity of inhibition of PDE V necessary to treat BPH.

The '124 Patent claims a "method for the prophylaxis or treatment of benign prostatic hyperplasia" by administering "an inhibitor of phosphodiesterase (PDE) V." The '124 Patent discloses several "preferred inhibitors of PDE I, PDE IV, and PDE V," but makes no distinction between those compounds that inhibit PDE V as opposed to other PDEs, such as PDE I and PDE IV. As noted above, the '124 Patent also does not disclose what potency or level of inhibition of PDE V is required or necessary to effectively treat BPH.

Furthermore, the Asserted Claims of the '124 Patent impermissibly covers future advances and discoveries (of, for example, new inhibitors of PDE V), including, for example, combination therapies, in the unpredictable field of chemical arts. In connection with the functional claim to any "inhibitor" of PDE V, the scope of the Asserted Claims impermissibly encompasses potentially millions of undisclosed embodiments of an inhibitor of PDE V, whether known or unknown at the time of the filing date, whether to be discovered later, and no matter

what level of inhibition or potency of inhibition. *See Promega Corp. v. Life Technologies, Corp.*, 773 F.3d 1338 (Fed. Cir. 2014) (claim not enabled where it covered "potentially thousands of undisclosed embodiments in an unpredictable field"); *Wyeth and Cordis Corp. v. Abbott Labs.*, 720 F.3d 1380 (Fed. Cir. 2013).

b) Invalidity for Lack of Written Description

The Asserted Claims of the '124 Patent are invalid under 35 U.S.C. § 112, ¶ 1 because there is an inadequate written description for the claimed "effective amount of an inhibitor of phosphodiesterase (PDE) V" sufficient or adequate for the prophylaxis or treatment of BPH. The '124 Patent purports to claim the genus of inhibitors of PDE V. However, the specification of the '124 Patent fails to provide an adequate written description to support this claim. "When a patent claims a genus using functional language, the specification must demonstrate the applicant has invented species sufficient to support a claim to the functionally-defined genus." *See AbbVie Deutschland GmbH & Co. v. Janssen Biotech, Inc.*, 759 F.3d 1285 (Fed. Cir. 2014). "[A]n adequate written description requires a precise definition, such as by structure, formula, chemical name, physical properties, or other properties, of species falling within the genus from other materials. *Ariad Pharmaceuticals, Inc. v. Eli Lily & Co.*, 598 F.3d 1336, 1350 (Fed. Cir. 2010). "A description of what a material does, rather than of what it is, usually does not suffice….The disclosure must allow one skilled in the art to visualize or recognize the identity of the subject matter purportedly described." *Enzo Biochem, Inc. v. Gen-Probe, Inc.*, 323 F.3d 956, 968 (Fed. Cir. 2002) (citing *Regents of the Univ. of California v. Eli Lilly & Co.*, 119 F.3d 1559, 1568 (Fed. Cir. 1997)). Moreover, "[r]egardless whether a compound is claimed *per se* or a method is claimed that entails the use of the compound, the inventor cannot lay claim to that subject matter unless he can provide a description of the compound sufficient to distinguish infringing

compounds from non-infringing compounds, or infringing methods from non-infringing methods." *Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 926 (Fed. Cir. 2004).

The claim to "an inhibitor of phosphodiesterase (PDE) V" is neither supported by a representative number of species of inhibitors of PDE V nor a disclosure of structure that correlates with the claimed function "inhibitor" of PDE V that is common to all members of the genus. A person of ordinary skill in the art would have known as of the filing date of July 19, 1997 that there are potentially millions of small molecule compounds that represent a large number of structurally distinct molecules, large molecule compounds including antibodies, and even naturally occurring products (such as those found in caffeinated drinks such as coffee or tea, fruits and vegetables) that could "inhibit" PDE V at some level. The specification's minimal disclosure of "preferred selective inhibitors of PDE I, IV and V" fails to disclose a representative number of species to support the claimed genus of inhibitors (selective and non-selective) of PDE V.

The specification's list of compounds stated as "preferred inhibitors of PDE I, PDE IV and PDE V" is inadequate to meet the written description requirement. The specification does not distinguish between which compounds inhibit which isoenzyme (PDE I, PDE IV or PDE V. In *Purdue Pharma L.P. v. Faulding, Inc.* 230 F.3d 1320 (Fed. Cir. 2000), the disputed claims recited an extended-release drug formulation requiring a certain ratio between the maximum blood concentration and its concentration 24 hours later. However, of the seven purported examples of the claim disclosed in the specification, only two could be shown to meet the claimed ratio limitation by piecing together the disclosed data. "[N]either the text accompanying the examples, nor the data, nor anything else in the specification in any way emphasize[d] the [claimed] ratio." *Id.* at 1326. *See also Novozymes v. DuPont Nutrition Biosciences*, 723 F.3d

1336 (Fed. Cir. 2013). Here, nothing in the text accompanying the examples, nor anything else in the specification, in any way emphasizes the claimed inhibition of PDE V as opposed to PDE I or PDE IV. Rather, the specification merely lists various compounds of different structures each with, apparently, some ability to inhibit PDE I, IV and/or V.

Moreover, the disclosed compounds—as well as undisclosed compounds (including the compound tadalafil that is the active ingredient in the Accused Instrumentality, Cialis)—vary substantially in molecular structure. A person of ordinary skill in the art would understand that there are no common chemical structural components representative of the claimed genus of all inhibitors of PDE V. A person of ordinary skill in the art would also understand, as of the filing date of July 19, 1997, that there is no correlation between chemical structure and the function of inhibiting PDE V (or PDE I or IV) that would be common to all members of the genus. The specification of the '124 Patent does not adequately describe the full scope of the functional genus claim to "an inhibitor of phosphodiesterase (PDE) V."

The Asserted Claims of the '124 Patent recite methods encompassing the outer limits of a purported genus of materials achieving a stated useful result, *i.e.*, inhibiting PDE V. But, as in *Ariad* and *Eli Lilly*, the specification does not disclose a variety of species that specifically stated to accomplish that result. The description of the term "inhibitor" (a generic and indefinite term itself), described even in terms of its function of inhibiting PDE V, is insufficient.

The Asserted Claims also are invalid under 35 U.S.C. § 112, ¶ 1 because there is an inadequate written description for the recited a negative limitation—"excluding a compound selected from the group consisting of …."—added by amendment during prosecution of the '124 Patent. Neither the specification of the '124 Patent, nor any earlier filed patent or application to which the '124 Patent claims priority, provides an adequate written description for this

limitation. To provide support for a negative claim limitation, the written description must describe, at a minimum, a reason to exclude the relevant limitation. *Santarus, Inc. v. Par Pharmaceutical, Inc.*, 694 F.3d 1344, 1351 (Fed. Cir. 2012). The negative limitation added by amendment in the Asserted Claims lacks an adequate written description as it is not supported by the specification, previous claims or prior related patents in the priority chain. *See Ex parte Grasselli*, 231 USPQ 393 (Bd. App. 1983), *aff'd* mem., 738 F.2d 453 (Fed. Cir. 1984).

2. Invalidity Under 35 U.S.C. § 112, ¶ 2

35 U.S.C. § 112 includes a definiteness requirement. See 35 U.S.C. § 112, ¶ 2 ("[T]he specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention."). In *Nautilus v.* v. *Biosig Instruments, Inc*., 134 S. Ct. 2120, 2124 (2014), the Supreme Court held that "a patent is invalid for indefiniteness if its claims, read in light of the specification delineating the patent, and the prosecution history, fail to inform, with reasonable certainty, those skilled in the art about the scope of the invention."

The Asserted Claims are indefinite under § 112, ¶ 2 because the follow claim terms or phrases are indefinite: "prophylaxis or treatment of benign prostatic hyperplasia"; "a patient in need thereof"; "inhibitor"; "inhibitor of phosphodiesterase (PDE) V"; and "effective amount of inhibitor of phosphodiesterase (PDE) V".

The '124 Patent does not disclose any method to select a PDE V inhibitor within the scope of the claimed invention or any particular level of inhibition activity required to be the claimed "inhibitor of phosphodiesterase (PDE) V" sufficient or adequate for the claimed method for the prophylaxis or treatment of BPH. Persons of ordinary skill in the art would understand that there are infinite potential compounds and infinite levels or measurements to determine whether a particular compound "inhibits" PDE V.

The claimed "inhibitor of phosphodiesterase (PDE) V" is indefinite as to whether *any* level of inhibition of PDE V is sufficient or whether inhibition of other PDEs (such as PDE I or PDE IV) is within the scope of the invention. The term "inhibitor" in the Asserted Claims necessarily is a term of degree (of inhibition) that fails to provide sufficient notice of its scope. In addition, a person of skill in the art would have understood, at the time of the filing of the application, that there were several ways to determine inhibition of PDE V, but that each of those ways, or assays, could provide fundamentally different results as to whether a compound inhibits PDE V and whether that compound also inhibits other PDEs. Because the assays that might be used to determine inhibition of a PDE do not always produce the same results, the assay chosen for determining whether a particular compound inhibits PDE V could affect whether or not a given compound infringes the claims. Neither the claims nor the specification of the '124 Patent provide any guidance as to a specific method that should be used to identify a claimed compound or to determine inhibition, or whether the possible universe of methods is reasonably limited (it is not). As a result, the claim limitation "inhibitor of phosphodiesterase (PDE) V" is indefinite and the Asserted Claims are therefore invalid. *See Dow Chem. CO. v. Nova Chems. Corp.*, 803 F.3d 620 (Fed. Cir. 2015).

The claimed limitation of "a patient in need thereof" in context of the claimed method for the "prophylaxis or treatment of benign prostatic hyperplasia" is also indefinite. The specification of the '124 Patent does not define "benign prostatic hypertrophy" but instead merely lists a variety of symptoms loosely associated with "prostatic diseases" as well as other organs (e.g., bladder instability and impotence). '124 Patent, Col. 2:17-27. There is no disclosure or teaching sufficient to inform, with reasonable certainty, a person of ordinary skill in the art as to how to determine and diagnose a person in need of prophylaxis (i.e., prevention) of BPH. At

most, the '124 Patent suggests that a benign growth of the prostate gland occurs in 50% of males of 50 years and above, "which may result in sever difficulties in the miction up to anuria and which is subject to treatment obligation." *Id.* at Col. 1:10-14. The mere suggestion that half the male population age 50 years and above may suffer from a benign growth in the prostate gland, which may result in difficulties in miction, is not sufficient to inform, with reasonable certainty, persons of ordinary skill in the art as to how to determine whether the claimed "person in need thereof" is, in fact, "in need" of prophylaxis or treatment for BPH.

The claim limitation "effective amount" of an inhibitor of PDE V is indefinite as well. There is no disclosure or teaching in the '124 Patent as to the specificity required of an inhibitor of PDE V sufficient to inform a person of ordinary skill in the art, especially in light of the multitude of assays known to measure selectivity and how those assays would provide different results. Nor is there any disclosure of the required potency to constitute "an effective amount" sufficient for the prophylaxis or treatment of BPH. All of these properties depend from the structure of the molecule itself. Given the substantial variance in the potential molecular structures of inhibitors of PDE V, the '124 Patent does not inform, with reasonable certainty, persons of ordinary skill in the art as to the scope of the limitation "effective amount" of an inhibitor of PDE V.

3. Invalidity Under 35 U.S.C. § 112, ¶ 6

A claim may be drafted in a manner that invokes 35 U.S.C. § 112, ¶ 6, which states:

> An element in a claim for a combination may be expressed as a means or step for performing a specified function without the recital of structure, material, or acts in support thereof, and such claim shall be construed to cover the corresponding structure, material, or acts described in the specification and equivalents thereof.

Merely because an element in a claim does not include the word "means" does not automatically prevent that element from being construed as a means-plus-function element. *Williamson v. Citrx*

Online LLC, 792 F.3d 1339, 1348 (Fed. Cir. 2015). "[T]he essential inquiry is not merely the presence of absence of the word 'means' but whether the words of the claim are understood by persons of ordinary skill in the art to have a sufficiently definite meaning as the name for the structure." *Id.* Section 112, para. 6 will, therefore, apply if the claim term fails to "recite sufficiently definite structure" or else recites "function without reciting sufficient structure for performing that function." *Id.* at 1349.

The Asserted Claims of the '124 Patent recite the administering to a person of "an inhibitor of phosphodiesterase (PDE) V" for the prophylaxis or treatment of BPH. The term "inhibitor" is defined solely by its function here—i.e., the inhibition of PDE V. The term "inhibitor" does not connote specific structure; it is nothing more than a black box that includes any substance, known or unknown, that performs the function of inhibiting PDE V. The Asserted Claims could just as easily recited the phrase "means for inhibiting PDE V." Accordingly, the term "inhibitor of phosphodiesterase (PDE) V" for the prophylaxis or treatment of BPH is subject to application of § 112, ¶ 6.

The next step is to determine whether the specification of the '124 Patent discloses sufficient structure corresponding to the claimed function of inhibiting PDE V. It does not. "Structure disclosed in the specification qualifies as 'corresponding structure' if the intrinsic evidence clearly links or associates that structure to the function recited in the claim." *Williamson*, 792 F.3d at 1352 (citing *Noah Sys., Inc. v. Intuit Inc.*, 675 F.3d 1302, 1311 (Fed. Cir. 2012)). Even if the specification discloses corresponding structure, the disclosure must be of "adequate" corresponding structure to achieve the claimed function. *Id.* If a person of ordinary skill in the art would be unable to recognize the structure in the specification and associate it

with the corresponding function in the claim, the means-plus-function claim is indefinite and, therefore, invalid. *Id.*

The specification of the '124 Patent fails to disclose any structure of a substance that is clearly linked or associated with the function of inhibiting PDE V for the prophylaxis or treatment of BPH. The structure disclosed in the '124 Patent is, at most, described as inhibitors of PDE I, PDE IV, and PDE V. Nowhere in the list of compounds or classes of compounds is there any description clearly linking them to the function of inhibiting specifically PDE V in order to prevent or treat BPH. At most, dependent claim 2 of the '124 Patent (which is unasserted) claims the compound zaprinast as capable of inhibiting PDE V for the prophylaxis or treatment of BPH. However, one of ordinary skill in the art would know that zaprinast also inhibits at least PDE I as well. There is nothing in the specification showing that zaprinast is "adequate" corresponding structure to achieve the claimed function of inhibiting PDE V for the prophylaxis or treatment of BPH.

Accordingly, the claim recitation of "an inhibitor of phosphodiesterase (PDE) V" is indefinite under § 112, ¶ 6.

V. INVALIDITY UNDER 35 U.S.C. 102(C) OR FORFEITURE OF PATENT RIGHTS

Defendants contend that the applicants to the '124 Patent abandoned the purported invention under 35 U.S.C. § 102(c) (pre-AIA) or have forfeited the purported invention. Section 102(c) (pre-AIA) provided that a person shall be entitled to a patent unless "he has abandoned the invention." Abandonment is a deliberate dedication of the invention to the public, either expressly or by necessary implication. Forfeiture results from the deliberate withholding of the invention from the public with the intent of extending the duration of the patent monopoly. *See Marvin Glass and Associates v. Sears, Roebuck & Co.*, 318 F. Supp. 1089, 1102-03 (S.D. Tex. 1970).

The record in the USPTO and foreign patent offices relating to the application that eventually issued as the '124 Patent, including prior related applications, reveals an intentional, negligent, and/or unexplained delay in seeking patent coverage for the claims now issued. *Electric Storage Battery Co. v. Shimadzu*, 59 S. Ct. 675, 681 (1939). A patent is not validly issued if the invention shown to have been abandoned, which may be evidenced by the express and voluntary declaration of the inventor, may be inferred from negligence or unexplained delay in making application for the patent, or may be declared as a consequence of the inventor's concealing his invention and delaying application for patent in an endeavor to extend the term of the patent protection beyond the period fixed by the statute. *Id.* A German patent application DE 195 40 642 was filed by some of the same named inventors on the face of the '124 patent in the German Patent Office on or about November 1, 1995. However, the German '642 application, which contained overlapping and similar disclosures as the application filed in July 1997, was never prosecuted or converted into a national stage application. There is no evidence of any prosecution of that application and, to the best of Defendants' knowledge, all the files relating to that application have been destroyed.

The record in the USPTO and other foreign patent offices also supports the applicants' forfeiture of the rights to obtain a patent by delaying prosecution in the USPTO or the other foreign patent offices. It has long been the rule that "[a]n inventor cannot without cause hold his application pending during a long period of years, leaving the public uncertain whether he intends ever to prosecute it, and keeping the field of his invention closed against other inventors." *Woodbury Patent Planning-Mach. Co. v. Keith*, 101 U.S. 479 (1879). The application for the '124 Patent was not filed until December 29, 2011—more than eight years after the '870 application filed on May 23, 2003, now U.S. Patent No. 8,106,061; more than fourteen years

after the '090 application based on application No. PCT/EP97/03617 filed on July 19, 1997, now abandoned; and more than sixteen years after filing of German application No. DE 19540642, which was never used as a priority document, and instead was abandoned and not prosecuted in any way. And, the '124 Patent did not issue until 2014—19 years after the German application was filed in November 1995. The lengthy history of delay and abandonment, before the USPTO and globally, demonstrates that the applicants improperly withheld the purported invention of the '124 Patent from the patenting process. This lengthy delay operates as a forfeiture of the right to a patent. *Levinson v. Nordskog Co.*, 301 F. Supp. 589, 591-92 (C.D. Cal. 1969) (ruling that inventor's five-plus year delay in filing his application operated as a forfeiture of the right to a patent).

VI. INVALIDITY UNDER 35 U.S.C. 101

Defendants contend that the Asserted Claims of the '124 Patent are directed to patent ineligible subject matter, namely a law of nature, and are therefore invalid under 35 U.S.C. § 101. In *Mayo Collaborative Servs. v. Prometheus Labs., Inc.* 132 S. Ct. 1289 (2012), the Supreme Court held invalid a method of treatment claim because the method of treatment claimed did nothing more than state a natural law governing the effects of a certain drug on the human body and add routine and conventional treatment steps by a physician.

In *Mayo*, the Supreme Court set forth a framework for distinguishing patents that claim laws of nature, natural phenomena, and abstract ideas from those that claim patent-eligible applications of those concepts. First, the court determines whether the claims at issue are directed to a patent-ineligible concept. *Id*. at 1297. If the answer is yes, then the court next considers the elements of each claim both individually and "as an ordered combination" to determine whether additional elements "transform the nature of the claim" into a patent-eligible application. *Id.* at 1298. The Supreme Court has described the second step of this analysis as a search for an

"inventive concept"—i.e., an element or combination of elements that is "sufficient to ensure that the patent in practice amounts to significantly more than a patent upon the [ineligible concept] itself." *Id.* at 1294; *see also Digitech Image Techs., LLC v. Elecs. For Imaging, Inc.*, 758 F.3d 1344, 1351 (Fed. Cir. 2014).

Defendants contend that, like in *Mayo*, the Asserted Claims are directed to a law of nature. The specification of the '124 Patent makes clear that the claims are directed to a the existence of a naturally occurring enzyme, PDE V, in the human body, namely the prostate (although the claims do not require even that), and the observation that PDE V is involved in the breakdown of cGMP which is second messenger involved in smooth muscle contraction and relaxation. The specification of the '124 Patent demonstrates that the claims are directed to a naturally occurring thing or naturally occurring phenomena—specifically, the assertion:

> Surprisingly, it has now been found that sPDE I, sPDE IV and sPDE V are of particular importance in human prostatic muscles: After performing Q-sepharose chromatography, there has been found a typical patter of the human prostatic tissue showing the presence of the PDE isoforms I, IV and V (below).

'124 Patent, Col. 2: 6-11. Further, according to the '124 Patent:

> The physiological transmission of information for the relaxation of smooth muscle cell is effected by messengers of the blood (hormones) or the nerves (neurotransmitters). These messengers and neurotransmitters cause an increase in the levels of the cyclic nucleotides "cyclic adenosine monophosphate" (cAMP) and "cyclic guanosine monophosphate" (cGMP) in the smooth muscle cell, resulting in relaxation. cAMP and cGMP themselves are hydrolyzed by phosphodiesterase's (PDEs). Inhibitors of PDEs in turn reduce the digestion of cAMP and cGMP, resulting in the increase of these molecules within the cell and thus in a relaxation of the smooth muscle cell.

Id. at Col. 1:36-47.

In the second step of the *Mayo* framework, the court examines the elements of the claim to determine whether the claim contains an inventive concept sufficient to "transform" the claimed naturally occurring phenomenon into a patent-eligible application. 132 S. Ct. at 1294.

Here, the practice of the method claims does not result in an inventive concept that transforms the natural phenomenon of the existence of PDE V in the human prostatic tissue and its effect on cGMP levels to control smooth muscle tone into a patentable invention.

Independent Claim 1 purports to claim merely "an inhibitor of phosphodiesterase (PDE) V" for the "prophylaxis or treatment of benign prostatic hypertrophy." This is very different from a method claim that involves administering a class of compounds defined by a structural formula. As noted above, it is a natural phenomena that PDE V exists in the prostate and plays a key role in the catalysis of cGMP in smooth muscle tissue. *Mayo* made clear that transformation of an otherwise natural law into a patent eligible concept requires "more than simply stat[ing] the law of nature while adding the words 'apply it.'" *Ariosa Diagnostics, Inc. v. Sequenom, Inc.*, 788 F.3d 1371, 1377 (Fed. Cir. 2015) (quoting *Mayo*, 132 S. Ct. at 1294). Here, the Asserted Claims merely reflect the natural phenomena that PDE V exists in the prostate and applies the words "inhibit it" so as to achieve the effect of smooth muscle relaxation. But methods of inhibiting PDE V were already well known in the art. *See Mayo*, 132 S. Ct. at 1298; *Sequenom*, 788 F.3d at 1377. Moreover, the claimed process of "administering" an "inhibitor" of PDE V amounts to "nothing significantly more than an instruction to doctors to apply the applicable laws when treating their patients." *Mayo*, 132 S. Ct. at 1298; *Sequenom*, 788 F.3d at 1377. "Simply appending conventional steps, specified at a high level of generality," is not enough to supply an inventive concept. *Mayo*, 132 S. Ct. at 1300; *Sequenom*, 788 F.3d at 1377. Merely limiting a natural law to a particular technological environment does not render the claim patent-eligible. *Mayo*, 132 S. Ct. at 1297.

Moreover, because the Asserted Claims are also directed to the "prophylaxis" of BPH, the breadth of claim to anything, known or unknown, that inhibits PDE V used by males is

essentially infinite but certainly unbounded by anything in the patent. The '124 Patent suggests that a benign growth of the prostate gland occurs in at least 50% of males of 50 years and above, "which may result in severe difficulties in the miction up to anuria and which is subject to treatment obligation." *Id.* at Col. 1:10-14. In addition, because many naturally occurring products have an inhibitory effect on PDE V, including many foodstuffs, fruits, vegetables, caffeine, and red wine that have been consumed for centuries by males age 50 and over, the patent is directed to centuries of activities by men. The claims at issue are directed to naturally occurring phenomena. Thus, at least half the male population over the age of 50 could be found to infringe the Asserted Claims simply by preventing BPH by ingesting any substance that happens to inhibit PDE V—including such ubiquitous natural products as red onion and many other plant extracts and natural products that are known to inhibit PDE V when consumed. Such preemption is improper and unpatentable: "[P]atent claims should not prevent the use of the basic building blocks of technology—abstract ideas, naturally occurring phenomena, and natural laws." *Sequenom*, 788 F.3d at 1379.

None of these infirmities illustrated with respect to Claim 1 is eliminated by elements of the remaining asserted claim 3, and thus Claim 3 falls together with Claim 1 for the same reason.

VII. ADDITIONAL RELEVANT ART

In addition to the prior art references described above, Defendants provide a non-exhaustive identification of materials pertinent to the '124 Patent at Exhibit B hereto.

VIII. ACCOMPANYING DOCUMENT PRODUCTION

Pursuant to Patente Rule 3-4(a), each Defendant has produced, or made available for inspection and copying, documents sufficient to show the elements of the Accused Instrumentality, Cialis® (tadalafil) as indicated for the treatment of the signs and symptoms of benign prostatic hyperplasia, including documents produced as Brookshire00000001-44 and

Lilly00000001-176. Pursuant to Patent Rule 3-4(b), Defendants are producing or making available for inspection copies of each item of prior art identified pursuant to Patent Rule 3-3(a) which does not appear in the file history of an Asserted Patent. To the extent that an item is not in English, an English translation is produced where available.

Dated: January 26, 2016

Respectfully submitted,

/s/ Todd G. Vare

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CERTIFICATE OF SERVICE

The undersigned hereby certifies that all counsel of record who are deemed to have consented to electronic service are being served with a copy of this document via electronic mail on January 26, 2016.

/s/ Todd G. Vare
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